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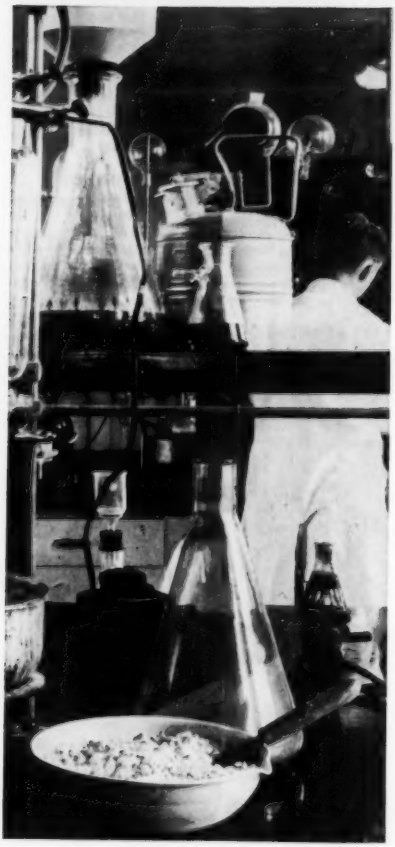

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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E D I T O R I A L

ONLY A PHARMACIST CAN DO IT WELL

AN EDITORIAL in the Summer 1959 issue of the *American Journal of Pharmaceutical Education* should be required reading by the top executives of every pharmaceutical company in the United States. The Editor, Dr. Melvin R. Gibson, outlines what is fast becoming a very critical problem and one which seems certain to cause irreparable harm to both the drug industry and the public alike. Dr. Gibson decries the trend of employing as medical service representatives persons who are totally unprepared for such work academically. In his editorial, he reports on a rather thorough study of this current trend and calls attention to what the eventual result will be in weakening the links between the manufacturer, physician, and pharmacist and the impact of this on public health and welfare. While we urge our readers to refer to Dr. Gibson's excellent editorial on this, we cannot help but comment on this very disturbing situation ourselves.

The drug industry in the last two decades has grown tremendously as almost everyone knows both within the industry and without. Not only has it grown in size from the standpoint of invested capital and sales, but it has grown just as much in the contribution which it makes to the over-all health of our people and in the proper functioning of the health professions. The physician today would be completely at a loss without the modern medicinal agents which are placed at his disposal and he knows by experience that he must keep well informed concerning the rapid new developments in medicinals. Without this knowledge, he is severely handicapped and may even be accused by his patients and fellow practitioners of being behind the times and using obsolete drugs.

There is no field of human endeavor anywhere in the world in which the rate of obsolescence is greater than in the field of medicinals. It has been the rapid pace with which new drugs have been developed which has contributed most to the tremendous strides in increasing life expectancy and the health and well-being of people the world over. The physician knows this and it is for this reason that he is highly receptive to those medical service representatives who keep him in-

formed of each new development and give him guidance in how best to adapt these new agents to his own type of practice or field of specialization. Whether the medical profession wishes to acknowledge it or not, the fact remains that most of their innovations in practice they gain not from the graduate medical schools or medical journals but from the medical service representatives who call on them regularly.

Those in our pharmaceutical companies who are entrusted with the task of translating new medicinal agents to the physician through the medical service representatives, and training such representatives know only too well how extremely difficult it is—if not impossible—to brief them thoroughly on these new drugs unless they are well grounded in such fields as physiology, biochemistry, medicinal chemistry, and pharmacology. Lacking such requisite knowledge, the most that can be accomplished is to teach them to recite, parrot-fashion, a "sales pitch" without having the slightest understanding of what it means and being even less prepared to discuss the matter informally with the physician. Such representatives sooner or later ruin the reputation of the manufacturer since they shake the confidence of the physician who hesitates to believe anything told him by such poorly informed individuals. It often appears that these representatives have memorized their "detail" since, if interrupted at any point, they have to back-track and start over just as does a child who has remembered some verses which he must recite.

Just recently, we were being "detailed" by a young fellow who quite obviously did not understand the new drug which he was describing. He was representing one of the largest pharmaceutical companies in the United States and it caused us no little surprise when we questioned him concerning his background to learn that he had taken business administration in college. Other representatives whom we have questioned have been found to be those who failed in premedical colleges, some with degrees in biology, and still others with no college experience at all.

This situation has grown out of the fact that those executives in pharmaceutical industry who are responsible for top policy decisions are usually themselves not pharmaceutically trained and not being so trained they fail to appreciate just what is needed by the medical service representative if he is truly to render the service to the physician which the physician expects and which good medical practice

requires. This is not simply a sales job. It takes a thoroughly grounded individual and not one who has just a smattering of technical terms which he does not understand and cannot be expected to understand regardless of his indoctrination and training. Today's complex medicinals just cannot be fully understood except by those who have had extensive college preparation in the field. We venture to say that only the well-trained pharmacist or physician is capable of understanding these drugs in the way that their scientific use and application requires.

While it is true that there is some shortage of pharmaceutically trained personnel, there does not need to be any shortage of good pharmaceutical service including a shortage of good medical service representatives. It is purely a matter of economics. Well-trained pharmacists are available and in almost any number desired providing those who wish such personnel are willing to pay the cost. Modern pharmaceutical training is an extremely difficult discipline and it cannot be made more easy if the graduate is to be properly prepared. The complexity of modern pharmaceuticals is not something which the schools of pharmacy have created but it is something which they must face, and face realistically. We could turn out vast numbers of so-called pharmacists by cheapening the training given and making it a technician's course rather than the solid course which it is. This, we shall not do. It remains for those who need pharmacists—and we feel need them very badly—to recognize their true worth and the essential place which they should and must fill in the distribution system for modern drugs. It seems to us rather poor economics for companies to spend millions of dollars in promoting their products to the medical profession only to have their impact lost and the reputation of their company damaged through the practice of having poorly educated persons as medical representatives. In their attempts to service the medical profession, they only expose their glaring weaknesses and total unfitness to give the physician the help and guidance which he so desperately needs.

Again, we suggest that those who have read this editorial read Dr. Gibson's treatment of this vital subject. The medical service representative in many instances may be the weakest link in our otherwise excellent distributive system. It should be our *strongest* and, with proper resolution, it can be made so.

L. F. Tice

THE NEW PRODUCT CHALLENGE *

By George B. Stone **

IN 1939, your graduates who operated the 53,500 retail pharmacies in these United States filled a total of 182,100,000 prescriptions.[1] Four out of five of these prescriptions were compounded on the premises. Last year (1958), according to the latest Drug Topics survey, 54,390 U. S. pharmacies filled 655,110,000 prescriptions. Nine out of ten of these were prefabricated by the drug manufacturers.

Formerly, the lion's share of manufacturers' products simply alleviated the symptoms of disease to make the patient more comfortable while nature took its course. Today, emphasis has shifted toward products which prevent or control illness—toward modern chemotherapy and specific treatment. So radical has been the change that about 90 per cent of the prescriptions being written today could not have been filled before World War II because the drugs were not available then.

Research and the prompt commercialization through the new product development procedure is fundamental to the pharmaceutical industry and accounts for the tremendous growth of the industry in the past 20 years—and for the individual successes of the various companies. Research, as you know, is expensive and frequently unrewarding. This year, it is estimated that the pharmaceutical industry will spend $190 million on research—more than 7 per cent of every sales dollar. You can contrast this percentage to the 1 or 2 per cent expenditure for the average of all industry. But, of course, the mere expenditure of money does not insure that anything useful to mankind will evolve.

Our efforts must be centered on those areas of therapy where the greatest need for improvement exists. To do this, we must consider

* Presented by Charles C. Rabe at the NPC Pharmacy Education-Industry Forum, Princeton, N. J., Aug. 25, 1959.

** General Manager, J. B. Roerig and Company, Division Chas. Pfizer & Co., Inc., New York, New York.

[1] Drug Topics Annual Surveys.

the incidence of various illnesses, their effect upon mankind in terms of mortality, disability, and confinement; we must be conscious also of the therapy being used in medical practice, the success of this therapy, and needs of the medical profession.

Because medical therapy is so diverse, no one company can successfully conduct research in all areas; it is for this reason that the industry is characterized by a comparatively large number of firms. *No industry in the country or indeed in the world spends a greater percentage of its sales dollar for the very elemental objective of making obsolete the products from which these dollars are realized.*

Every year the pharmaceutical industry spends more and more of its sales dollars for research. It might surprise you to know that the owners of pharmaceutical companies, the share owners, currently receive in dividends an amount totaling only slightly more than the money plowed back into medical research for tomorrow's products.

New product development is a long, tedious, complex pathway more frequently beset with failures than with successes. The mere discovery of a new chemical compound which reveals a certain therapeutic action is not enough. Last year, for instance, more than 100,000 products were tested biologically or pharmacologically by the industry; about 2,000 were tested clinically in man, but only about 400 new products resulted and only about 20 of these were basically new chemical entities. For example, 5,000 analgesics have been discovered, but only eight are in common use; more than 4,000 antibiotics have been isolated, but only about two dozen have been marketed; of 14,000 compounds which have been tested for antimalarial potency, only about three or four are satisfactory for human use.

To insure safety, millions of trials in animals must be undertaken to establish potency, toxicity, and contraindications. If the drug passes all of these tests with flying colors, the whole trial process must be repeated in the clinics under carefully controlled and observed conditions. In the development of one of the new oral drugs for treatment of diabetes, for example, more than one million patient-days went into the clinical program alone. Before a drug can be offered to the medical profession, the results of these experimental trials must gain the acceptance of the Food and Drug Administration. Add to this the requirements of many foreign governments which must be adhered to for marketing a product in countries outside the United

States and, in addition, the accumulation of scientific data in most of these countries in order to demonstrate to physicians that the drug is efficacious, and you can see the multiplicity of the problem. Incidentally, in order to sell pharmaceutical products in most foreign countries, it is necessary to carry out this clinical work in those particular countries as physicians usually prefer scientific data collected by their own colleagues. Right now, many manufacturers have clinical programs going not only in every state of the United States, but also in almost every foreign country. Coordinating these programs and transposing them into publications for use by the medical profession poses a great task in itself. Thus, when a new drug becomes available, the physician must be informed in such a way as to satisfy his own scientific criteria.

The mechanical details in the successful development of a new pharmaceutical product range all the way from package size to palatability, from toxicity to tablet form, from new drug application to retailer announcement. In this story, the pharmacist plays a leading role. Certainly, many of your students will find their way into the industry and will participate, no matter what their position, in some phase of the development of a new drug product.

Almost every successful new product has its origin in long-range research planning but the initial impetus may arise in very diverse areas of the companies involved. Marketing research, for example, often initiates the development of new drugs by exposing a demand which was previously unsuspected. The clinical research department may notice that physicians in general find existing products in a particular area unsatisfactory. It also often happens that a chemist takes a long, close look at an existing product—quite frequently one made by his own company—and sees in its molecular structure those challenging reactive sites which tell him that perhaps it can be modified and improved.

One of the simplest ways in which a new product may come about is through the observation of prescriptions. When a manufacturer's clinical research department sees that many physicians are prescribing several different drugs for the treatment of a given condition, it is common sense for the manufacturer to offer these various ingredients in a single tablet or capsule. For example, meclizine hydrochloride and nicotinic acid, two drugs with quite different sites of action but a common beneficial effect, were combined in a successful product for

the management of vertigo and Meniere's Syndrome. Sometimes, too, the development of one new class of drug will stimulate the development of a different class; for example, we never really understood how widespread the problem of depression was until the advent of the tranquilizers. These drugs help many mental patients but significantly do little good for the depressed. Thus, a problem was spotlighted and the stage set for the search for anti-depressive agents.

In this area, too, there is the role of accident combined with sharp observation which is sometimes called "serendipity" after Walpole's three princes of Serendip who were constantly turning near calamity to advantage. But I prefer not to use the word since it tends to stress the accidental and underplay the role of observation.

Chance, as Louis Pasteur said, favors the prepared mind, and there are few finer examples of this than the discovery of the anti-depressive action of iproniazid. This drug was being given experimentally in the chemotherapy of tuberculosis, and nobody had any reason to suspect that it would have any effect whatsoever on the mood of the patients. The fact that it did exert such an effect was noted, however, by the clinicians involved and, before long, hundreds of related drugs were under test in pharmaceutical company laboratories. In our own laboratories, we were happy to discover that hydroxyzine hydrochloride, a tranquilizer, also exerted anti-secretory, anti-arrhythmic, antihistaminic, and anti-serotonic properties, all of them clinically useful, and none of them expected in the light of our original objectives.

Having determined the major areas of interest and the funds at hand, a company sets up the pharmacological screens and programs required to evaluate the chemical fruits of its own research . . . or the compounds derived from any other available source. Money must often be spent for research on the screen itself to find a test which will point to promising chemical compounds, especially in areas where existing screening techniques are considered imperfect or unsuitable. Typical examples today would be cancer, the collagen diseases such as arthritis and rheumatism, mental disease, heart and cardiovascular diseases.

A successful new test or screening technique often actually insures the development of a new product. In fact, many of the modern chemotherapeutic successes and most of the dramatic breakthroughs followed on the heels of a new test or a screen that was good

—and cheap. Thus, most of the new corticoid hormones were developed as a result of a screening technique involving implant tests in rats, and most of the antibiotics after penicillin were isolated after the plate testing technique was adopted as a large-scale screening device.

Once the screen has been devised, it is used to review as many chemical compounds as possible, as inexpensively as possible. Scientists at one cancer research center are working on both ends of this problem at once; that is, they are screening new compounds—mostly antibiotic broths—by several recognized methods while, at the same time, investigating new screening methods which may prove more sensitive than those presently in use. One such method, involving the use of cancer cells maintained in tissue culture, appears to be promising and may be useful as a check for the conventional screens utilizing rats and mice. There is also some hope that it may turn out to be a useful primary screen since it is relatively fast and inexpensive.

Out of the screen will come a number of promising candidates which demonstrate preliminary activity. I might add that all of these screens are either test tube or, more probably and more importantly, animal. The next step is to test the animal toxicity of these candidates so that a rough idea of their therapeutic index in various species can be determined. And then, we kiss most of the contenders goodbye because they are too toxic.

Let us assume, however, that out of this screening and toxicity testing comes a promising compound for some specific indications. At this point, a whole series of activities is initiated involving many disciplines. Immediately, additional toxicity and pharmacology studies are begun. Now, we have to know quite a lot more about safety and efficacy to make preliminary and careful human trials. Pharmaceutical Research will be called in to develop suitable dosage forms—whether tablet, capsule, parenteral, or topical—or perhaps, eventually, all four. Enter now process development—to work out various ways of producing the drug in bulk . . . and also in the dosage forms which may be approved. This may entail designing and building new equipment or redesigning existing facilities. Much of this work will go on even though few or no trials have yet been made in humans.

Work begins almost as quickly on one of the trickiest steps of new product evolution—the search for a name or often two names,

trade and generic. Marketing research steps in to make a preliminary survey of the current market, the pricing, the competitive products, the package sizes, and all the other factors which enter into the total marketing picture. Testing procedures for potency and safety must be developed and specifications established for routine study and acceptance of the basic compound and the dosage form or forms. But, assuming the new drug has passed these hurdles and still looks promising, very careful clinical evaluation commences. It is surprising—and often disappointing—that, with all our knowledge of pharmacology and toxicity in animals, we still cannot translate results and conclusions into the human. So, again, the majority of new drugs which work in animals fail in humans.

Suppose, however, that our new drug successfully bridges the gap from the lower vertebrates to homo sapiens. At this point, still another new series of activities is begun. Preliminary marketing plans are mapped out. The marketing research program is re-evaluated in relation to the existing market. A more complete study is made of the indications. For whom is the drug intended? Who is going to prescribe it? What about the ultimate consumer—who is he; how old is he; what, literally, are his tastes?

Still further studies of package size and pricing influence decisions about the size, design, and wording on the package, the carton, the label, and the package insert. Data necessary for a new drug application is compiled in earnest now not only in terms of safety and efficacy but as concerns specifications, indications, claims relevant to the package insert, brochures, and container. Preliminary marketing tests may be made on the dosage form and package size and also sometimes on palatability and patient acceptance.

Then, a careful analysis is made of production cost—and projected into the future in relation to the market potential for the drug. So a pricing schedule is established.

Now, we actually draft a preliminary profit and loss statement in accordance with the sales estimates furnished by the sales and marketing departments. A general theme is developed for the advertising and promotional introduction and for the marketing in the first six months to one year following introduction. The advertising and promotional program is blueprinted and carefully studied and reviewed. Out of this will come the plans for the monies to be

expended for journal advertising, for direct mail, for sampling, and for introduction notices to wholesalers, retailers, and hospitals.

Inherent in this program is the plan of action as it relates to the medical service representative or detail man in the field. There are some 15,000 men employed in this capacity in the United States. Their job is to keep 200,000 physicians informed on new drug therapy and to make sure that the 5,000 hospitals, 50,000 retail pharmacies, and 400 general line wholesalers know what the doctor wants. Supporting the detail man in communicating research results are advertisements in journals for the medical and allied health professions. These range from national publications, some of which reach 150,000 physicians per issue, to local bulletins with circulations of less than 500. This kind of media blankets vast audiences of physicians faster, though often less satisfactorily than the detail force.

While the sales division is involved in the marketing program, the clinical program—sufficient to obtain a new drug application—will probably be drawing to a close. Following submission of the New Drug Application with a view towards marketing and production schedules, a product introduction date will have been tentatively established. Plans for selling the product to the sales force will have been formulated and a training and introduction meeting will have been set up.

The day comes when the product goes to market and you sit back and hold your breath. For the first few weeks—or even months—it may be difficult to determine whether you have placed a winner or an "also ran." Industry-wide surveys show that in spite of all the exacting techniques developed by marketing research, four out of seven new products are not successful, two show some kind of profit, and one makes a real contribution. Some surveys indicate that 60 per cent of new products fail to bring a return on the manufacturer's investment.

From start to finish, developing a new product and getting it to market takes anywhere from eight or nine months to many years. This whole scheme of new product development—which is the real heart of the pharmaceutical industry—presents an ever-increasing challenge not only to the individual company and to the industry but to every member who is involved in these operations. At one time or another in the historical development of a new product, a great number of people and disciplines become involved—but the phar-

macist plays one of the largest number of roles of any professionally trained person in our industry.

Pharmacists almost completely staff the pharmaceutical research and development departments of all the drug companies. They compound the tablets, formulate the oral suspensions, and derive the topical and parenteral preparations. *They alone* successfully devise the dosage forms which find their way onto the shelves of every retail and hospital pharmacy. Pharmacists find their way into the production departments of drug companies and become supervisors and managers of the pharmaceutical production departments. You will find your former students in almost every pharmaceutical division in the industry—in marketing research and packaging departments, in sales divisions . . . and, because many of these men are business-minded, you will also find them in the management of these firms.

Because new product development has such a profound effect on the structure of business, it is usually a direct responsibility of top management. However, management needs help in exercising this responsibility. Business in all its aspects has become so complex that it now is imperative to organize the product development function.

To help develop these new products and to prevent any delays, the leading companies in the industry have set up new product coordination departments, often as part of their commercial development divisions. The department usually works with all divisions of the company; yet, does no research work, no development work, no production work, and no selling—except selling management on bringing out new products. Considering the investment and the risks involved in developing new products, it is no wonder that a strong case must be made for any new product before management will give the go ahead signal.

The job of new product coordinators is sometimes described as "coordinating." Their talents are time and energy—and their value can't be measured in dollars and cents. The New Product Coordination Department usually issues no orders of its own, but checks to see if orders from other departments have been carried out. In theory, if orders have not been given, the coordination department must report to the proper people so the orders can be given but, in actual practice, the department rarely does this. That is because the staff members involved know that developing new products is a give-and-

take situation and that new ideas cannot be developed without cooperation.

To get the job done, the coordinators must use tact, diplomacy, and extreme care in working with people. Success also hinges on having the current status of each new product readily at hand. This may be no problem for any one product. But just assume that there are a hundred check points or hurdles for each new product—actually, there may be anywhere from 50 to 200 development steps. Assume also that there are some 250 products at various stages of development, each with 100 check points—and, if your head will stop spinning, you begin to get the idea. Technical understanding of the whole procedure from research screening to marketing introduction is essential for anyone concerned with the coordination of new products.

One of the functions of New Product Coordination is to gain agreement on the priority of the many development jobs and to check to see that these priorities are observed and continuously reviewed. Because times and conditions are always changing, the department is always emphasizing and de-emphasizing certain projects in relation to the latest information and over-all objectives. Coordinators must reconcile conflicting views and check that all decisions are made promptly so that the new products can be developed without any difficulties. Otherwise, our laboratories could easily become crowded with various development projects and only a few products would ever be brought to market.

Once a new product is put on the market, we have to keep track of its sales. Detailed reports are frequently compiled of sales, and comparisons are made with the original estimates. In addition, Marketing Research carefully analyzes the sales figures as to region and general product acceptance. With this data, management can review the product's performance and decide upon appropriate measures if it isn't performing properly.

The department also has a year round responsibility to act as the company clearing house for new product ideas from management, research, sales, advertising, production, purchasing, quality control, accounting, legal, and other departments. Our management found that in developing new products the normal channels of communication between the divisions were too slow. So the New Product Coordination Department now gathers all the needed data, examines

and disperses it to the appropriate divisions for further action. But coordinators must always be on the lookout to avoid pitfalls and their accompanying problems, such as ending up with "scientific triumphs" that have no commercial application or products that work fine—in test tubes. Once in a blue moon, we run across compounds that don't work very well at all in test tubes but do a remarkable job where they're supposed to work—in humans.

Two out of every three products we sell were unknown less than 10 years ago. By 1970, just to maintain its competitive position, a pharmaceutical manufacturer will probably have to produce six new products for every four it sells today—maybe even more, considering the fantastic growth of the drug and chemical industries in the last five years. In today's market, product plans are the charts of competitive strategy and the departure points for corporate growth. In the pharmaceutical and chemical industries, new products are the "keys to the kingdom."

ETHICAL PHARMACEUTICAL PROMOTION *

By Tobias Wagner **

IN addressing this distinguished audience—composed of the successors of such world-famous pharmacists as Scheele, the first man to isolate oxygen, and Klaproth, discoverer of uranium—I am acutely conscious that you gentlemen are the educators of the men who ultimately dispense all the products that the ethical pharmaceutical industry makes. Consequently, I could scarcely be addressing a group of more vital importance to the industry in which I work.

Those engaged in the promotional activities of the ethical pharmaceutical companies are only human. They make, let it be admitted, their share of mistakes, calling down upon their heads the righteous wrath of this group or that. They succumb, occasionally, to overeagerness and fall into exaggeration (and my own company is no exception). But let it constantly be remembered that they are very like men earnestly trying to perform intricate juggling tricks while tightly trussed up in straight jackets. They must address their efforts to one of the most educated and highly critical audiences in the world, the U. S. health professions; they must at all times adjust their message to the professional attitudes of the physician; they must hew to the lines laid down by the Food and Drug Administration; they must avoid doing anything to offend the retail drug trade; they must not, in the case of O-T-C preparations, run counter to any regulation of the Federal Trade Commission; they must often, in the case of medical journal advertising, conform their copy to the editorial policy of the American Medical Association or of other medical groups; they must keep their fingers on the pulse of medical literature; they must be ready to modify their most precious claims in accord with ever-changing clinical findings; they must accept the restrictions imposed on them by their own research and development people; and they must avoid any comparison with their competitors' products which

* Presented at the NPC Pharmacy Education-Industry Forum, Princeton, N. J., Aug. 25, 1959.

** Director of Advertising, Smith Kline & French Laboratories, Philadelphia, Pa.

might be considered derogatory. They must do all these things and still sell goods in a highly competitive market. It's a tall order.

These drastic restrictions are among the reasons why ethical pharmaceutical promotion differs so markedly from all other types of promotion. But they constitute only one of the reasons, and I think not the most important one. The most important respect in which ethical pharmaceutical promotion differs from consumer promotion to the laity is that it is dedicated almost as much to educating and imparting essential information as it is to selling. Wallace Werble, editor of the *F-D-C Reports*, wrote some years ago, by way of warning to those who might be seeking to control or curtail pharmaceutical advertising: "Another fact cannot be overlooked: M. D.'s can't practice medicine today without the industry and its advertising and its constant stream of important new products." And Aims C. McGuiness, Special Assistant to the Secretary of Health, Education, and Welfare, stated in an address some years ago: "The educational force of this mass of promotional material is bound to be tremendous. I am sure that for many physicians this is the primary source of new professional information."

It is alarmingly clear that, occupying such a position on the national health team, pharmaceutical promotion should be like Caesar's wife: beyond suspicion. It isn't, of course, all of it beyond suspicion today; but it better get that way mighty quick if it is going to survive intact to escape the strangling controls of bureaucracy and to truly serve and be indispensable to the practicing physician.

Let me use a perhaps clumsy analogy. If automotive advertising were to be constructed along the lines of pharmaceutical advertising, you might come across an automotive advertisement which reads somewhat as follows:

> "The Mammoth Super-Eight brings you power, speed, incomparable comfort. To own one is an unprecedented adventure in modern motoring.
>
> "The Mammoth Super-Eight has everything. However, it is more than ordinarily prone to a peculiar kind of carburetor trouble . . . and also the storage battery tends to run down prematurely, occasionally leaving you stranded on a distant country road.

"The following page tells you in detail how to cope with these troubles should they occur.

"Furthermore, if not driven with due care and skill, the Mammoth Super-Eight may involve you in collisions which can result in serious injury and even loss of life. It is essential that you know exactly how to operate the Mammoth Super-Eight before even considering driving it. To this end, the following four pages (which we have bought and paid for for your benefit) give in explicit detail full instructions for operating the Mammoth Super-Eight. These pages should be read attentively and all cautions and warnings should be heeded."

You may laugh at this advertising travesty, but you will find many new drug circulars which read more alarmingly than this. In fact, hundreds of thousands of dollars are spent by the members of the pharmaceutical industry every year to outline painstakingly the inherent toxicities of drugs; their possible side effects, extremely rare though some of these may be; the contraindications to their use; and even the exact measures to be taken in the event that the patient is adversely affected by them. Let me cite some cases. I find that, in the early direct mail advertising on "Thorazine," the company spent almost $130,000 on eight special mailings primarily and almost totally devoted to discussion of the hazards attending the use of this drug (and this figure does not take into account many hours of the company president's costly time). Years later, $20,000 was spent on a single mailing on neurological complications of "Compazine" therapy. And, last year, $25,000, exclusive of the cost of distribution and showing, went into a film for mental hospital personnel on "Stelazine"—a film made almost wholly to depict the extrapyramidal side effects to be expected from high dosage of the drug. I don't think many people have any idea of all the time and money and human effort which are annually plowed into this sort of thing by the pharmaceutical companies.

Nor are the purely negative passages, devoted to inherent dangers, the only "non-selling" portions of pharmaceutical literature. Many product circulars will have page after page, re-run after re-run, covering nothing but chemistry, pharmacology, directions for administration and dosage, etc.—all this completely devoid of "sell." Strenuous effort and meticulous care go into these educational sections

of the literature and they often receive every bit the same attention by top management personnel as does the dynamically commercial copy.

I have tried to give you a little feeling of the peculiar quality of pharmaceutical promotion. I will now take up its main categories and touch on a few of the questions which I suspect are in your minds.

Besides such relatively minor activities as convention exhibits, films, closed-circuit TV, and regional symposia on drugs, there are three main divisions of professional promotion: detailing, direct mail, and journal advertising. I name these three in order of the money usually spent on them, although for some companies, of course, this order does not hold.

Detailing is perhaps the most effective form of pharmaceutical promotion and, although the most costly, it undoubtedly enjoys the highest degree of acceptance among M. D.'s. A study done a few years ago by the *Journal of the American Medical Association* revealed that 74% of physicians see all detailmen who call on them and another 22% see representatives from selected companies. Only 4% refuse to see any detailmen. A record of this sort could never have been achieved with such a discriminating and sophisticated audience if these detailmen had relied solely on the huckster's pitch instead of serving as one of the most reliable sources of medical information at the doctor's command.

These detailmen reach the physician in an indirect way, too. They cover all the pharmacies, educating their professional personnel to be able promptly and fully to supply the product information so frequently requested of them by physicians. At a conservative estimate, the pharmaceutical industry as a whole spends, in detailing, almost $4,000 a year on each of these pharmacies, large or small. And this figure is exclusive of the very considerable money spent on direct mail coverage.

But to go back—why the amazing popularity of the detailman? Well, first, he is selected with scrupulous care for intelligence, education, stability, maturity, and engaging personality. Then, he is intensively (and expensively) trained in medical background, particularly as it relates to his company's products. He invests promotion with the human approach, for which there is no substitute. His visits have the advantage of the face-to-face interview and of two-way communication. The average time he spends with his prospect on each call is only about 8 minutes. But, in this short time, he can do what

medical journal ads and direct mail cannot do; he can answer questions which these two media can never fully anticipate; he can reinforce confidence in his product by perceiving and resolving many of the doubts that inevitably linger in the doctor's mind. This on-the-spot status of his is a unique advantage. It has been well said that the physician can't ask questions of a brochure, neither can he argue with a descriptive circular. But, when the detailman calls, the physician considers him a living, breathing encyclopedia on all products and policies of that detailman's company.

But, like every medium of pharmaceutical promotion, detailing has its limitations. As I've mentioned before, it costs a lot—between $9 and $10 for every doctor visit. Furthermore, even with the hypothetically maximum detail force, it would be impossible, practically and economically, to reach all of the 200,000 odd doctors in the U. S. A. in any given detailing period. In addition, not even the most fast-talking detailman can give anything like the full story on his drug in the few precious minutes allotted to each M. D. And lastly, and perhaps most significantly, the best detailman can see only six or seven physicians a day, so that literally weeks may elapse between his first doctor-call with a given new detail and the last doctor he can tackle with that same detail before his efforts are switched to another product (and even at that point he will probably by no means have contacted the full list of doctors in his territory).

Now, let us turn to direct mail. It has its limitations, too; but it also has its own distinct advantages.

First, if the company is wise enough not to over-advertise, direct mail is less costly than detailing. (And, here, let me digress a moment. You might as well know, if you don't, that direct mail is the physician's favorite whipping boy; he habitually brands it as inordinately expensive and as a chief factor contributing to the high cost of drugs; but, ironically, he rarely, if ever, in his censures utters a word against detailing, the more expensive operation of the two.)

Secondly, nothing opens the doctor's door to the detailman like direct mail. The doctor cannot advantageously discuss, or even criticize, a product unless he first knows something about it. Thus, in many company programs, direct mail paves the way for the detailman's arrival.

Thirdly, direct mail is flexible, not rigid. If you find that you set your sights too high, if sales don't live up to expectations, you can rapidly reduce your direct mail or even, in the case of certain products, cut it out altogether. On the other hand, with detailing, you are fully committed to a fixed establishment; you can't cut back when the going gets tough unless you want to fire a lot of valuable, loyal men whom you can never get back. Or, conversely, if you are to keep your organization intact in a real slump, you must somehow keep your detailmen occupied on some assignment or other, even if the program proves unprofitable.

Fourthly, direct mail can get to more physicians faster than any other form of promotion. In contrast to a detail, a direct mailing can reach almost all the physicians in the country and it can reach them at almost the same time. These features are of incalculable value in the case of new product introductions and special announcements on already established products.

And, lastly, an indispensable function of direct mail is to reach the retail pharmacists on a nation-wide basis with new product information well in advance of the announcement to the physicians. This function of direct mail virtually guarantees that these pharmacies will be stocked to fill the first prescriptions they receive and will be prepared to perform their extremely important function of answering all physicians' queries intelligently.

Direct mail is without doubt the most kaleidoscopic medium of pharmaceutical promotion. Its variations are almost inexhaustible. It runs the gamut from, at one end, the simple government post card or double-sheet self-mailer with a brief reminder message on a single clinical aspect of the preparation to, at the other end, the comprehensive illustrated book, bound in stiff covers, containing a complete review—pathological, pharmacological, and clinical—on an important drug. In between these, there are many gradations: for example, envelope mailings containing a summary letter, a complete descriptive circular, and one or more reprints of scientific articles; box mailings containing an insert card with a telegraphic message, a folder tabulating clinical results in a leading indication, and a tear-off-strip dispensing sample; mailings with feature enclosures such as pads of diet charts for patient distribution; outsized house organs with 4-color

process printing, punctuated with advertisements of the company's chief products. In short, there is this to remember about direct mail: it needn't always, by any means, tell the complete story on a drug but, when it needs to, it always can. And careful surveys tell us that many of the complete-story pieces are retained in the M. D.'s bookshelves, along with his medical textbooks, for future reference.

Perhaps the biggest problem inherent in pharmaceutical promotion is the sheer bulk of the direct mail received by the physician. Last year, according to one reliable source, there was a slight decrease in total mailings: 3,902 (comprising 6,513 pieces), as against 4,041 (comprising 6,824 pieces) in 1957. But the volume is still formidable.

As to this problem, the industry keeps a sensitive ear attuned to the reactions, favorable and unfavorable, of the medical profession. And, more frequently than any other complaint, it hears the aggrieved cry: "Why do you send me so much stuff that is not applicable to my practice and in which I have little or no interest?" Certainly, the best step towards a satisfactory solution of this complaint is scrupulous list planning for each and every mailing to make sure that the pediatrician does not receive material on a geriatric preparation nor the dermatologist get mailings on a peptic ulcer remedy. More and more, the lists are being narrowly scanned in the hope that this pitfall may be avoided and that the physician may not become incensed at obvious waste, exasperated with encroachment on his time, and skeptical as to whether the company knows what it is doing.

There are other measures, too, constantly being investigated. For instance, the advent of automation, such as electronic data processing, promises future refinements of lists never before believed possible. For one thing, we may be able soon to cut out those physicians who have expressed to detailmen no intention of ever using a particular product or type of product. We are already able to withhold direct mail sampling from all physicians who are being or have recently been sampled on a specific product by the detailmen. Our addressings are sure to grow, year by year, more elaborately selective. In short, there is every likelihood that the present volume and the present percentage of waste and annoyance will be continually cut down.

I would now like to touch briefly on the third major segment of pharmaceutical promotion: journal advertising. Medical journal advertising, I think, is looked upon with decided favor by the M. D.

This is not hard to understand when it is remembered that most of the medical journals from which the physician gleans the latest developments in practice are largely supported by advertising. Furthermore, there is an impression on the part of the medical profession, usually entirely correct, that the ads in the journal he reads have received some sort of clearance from a constituted body of censors composed of physicans like himself. In addition, the journal advertisement takes on a certain psychological aura of authority by running cheek by jowl with scientific and expert editorial matter.

Once—not long ago—this journal advertising consisted mostly of full or half pages, or double-page spreads, which were essentially appealing eye-stoppers contrived primarily to remind the doctor of the product name and of an effective medical application of the drug. Product name, specific use, and claims for effectiveness, supported by brief copy, were the traditional components.

Today, there has been a surprising expansion of this concept. Multi-page advertisements have become common. Some of these actually assume the proportions of exhaustive monographs on the product, running to many pages, printed by the company and delivered to the publication for binding in what is called an "insert." An outstanding example of this was Pfizer Laboratories' monograph (it would be an understatement to call it an "advertisement") which appeared last fall in the *Journal of the American Medical Association* on their antidiabetic agent, "Diabinese." Here, in the pages of a medical journal, was a complete document the dissemination of which could once have been handled only by direct mail or detailing—a document sufficient to satisfy most of the demands of the medical practitioner. Indeed, today, journal advertising has assumed some of the tremendous flexibility of direct mail: a company has a range of choice running all the way between a telegraphic message in black and white on a quarter page and a comprehensive booklet carried as an insert (if it feels it can afford total costs of something like $48,000 per single insertion in the Journal of the A. M. A. alone!).

I cannot dwell longer on the medium of journal advertising. But I would do it injustice if I failed to mention its outstanding position as regards design. In typography, in layout, in illustration, and in functional use of color, pharmaceutical medical journal advertising is looked upon with admiration and some envy by the entire advertising

industry and artistic fraternity which accord it the highest merit as commercial art.

I have touched upon the three major media of pharmaceutical promotion and said they do an outstanding job of educating, informing, and selling. This statement may sound like the fond infatuation of a promotion man for the wares of his trade. But it isn't just a fond infatuation. It is backed by the findings of test after test, by the results of the most modern techniques of inquiry available.

We have a "divine discontent" with what we are doing in promotion. Relentless examination, based on the refusal to believe that what we do must be good just because we do it and like it, is carried out by our own internal marketing research departments and by numberless outside research concerns. We use the personal interview survey by our own men, the survey by the outside research agency, the direct mail questionnaire technique, case record studies; in short, every available method which we believe reliable. Shortly after the introduction of a new product, we receive in my company an accurate estimate of the familiarity with that product, the impression produced by our direct mail promotion on it, the acceptance and use already gained, the possible potential use by those who have not yet tried it but imply they intend to, the indications it has been used for, the manner of its use and the dosages employed, the results obtained, the incidence of side reactions encountered and how they relate to the dosage levels used, the reasons for favorable and unfavorable regard. All this data is collected, discussed, and summarized; on it are based considerable revisions of the original promotional material and much of our planning for future promotion. But always one incontrovertible fact emerges: intelligently planned, conscientiously executed ethical promotion does sell goods. We *know*, from factual, objective measurement, that pharmaceutical promotion is not just a soul-satisfying aesthetic activity carried on to inflate our own egos and hypnotize ourselves with the sound of our own words, but rather an indispensable activity of the industry without which the contributions of research would often languish in obscurity. This business of pharmaceutical promotion is not just an extravagant experiment; it is a proven technique without which the pharmaceutical industry could not continue, but which we never cease to scrutinize critically.

And now I feel that I should take up the sometimes misunderstood subject of sampling, a major activity shared by the detailing

and direct mail operations in varying ratios depending on the company's policy. At the outset here, I should like to make an admission, underline an economic law, and indulge in a metaphor. The admission is that there *is* such a sin as oversampling and that all of us in the industry have occasionally been guilty of it. The law, which we will call "Wagner's Law," is that whenever a member of the industry kills a sale for the retail pharmacist it also kills a sale for itself (and this industry has a positively psychoneurotic aversion to lost sales). And the metaphor: pharmaceutical sampling is seed sown for the sole purpose of raising up a bumper crop of prescription sales.

Like anything else, a sampling operation badly conducted can be a bad thing—it can kill sales! But a sampling operation correctly planned—the right kind and size of samples for the particular product, the right number of them for a year's campaign, distributed at the right intervals to the right doctors in the right way—can markedly stimulate sales.

My company knows this for sure. We have special reason to study sampling for, on the average, the percentage of our direct mailings devoted to sampling has been, over the past five years, more than three times greater than that of the industry as a whole. Consequently, we have subjected our sampling operation, both direct mail and detailing, to a continuing battery of tests.

Very briefly, this is the basis of these tests: a good many years ago, our Marketing Research Department divided the nation into twenty geographic marketing areas. They have studied these areas carefully and today they know the sales histories of various kinds of products in each of them well enough so that they are able to predict pretty accurately what a given product will do in each of them. Thus, by changing the promotional pattern in one or more areas where sales follow the national pattern and by analyzing the sales results against the baseline of national sales, they can gauge with reasonable assurance the degree of effectiveness of the promotion used.

First of all, we found that *samples do produce increased sales.* This fact was brought out by a series of reverse experiments. We chose appropriate test markets and to these we sent complete literature only—no samples at all. We did this with a number of different products—most particularly, new products. Our results were encouragingly consistent. *The unavoidable conclusion to be drawn from*

them is that we can sell only about one-half as much of a product in the first year without sampling as we can sell with sampling.

Second, we have found that, as long as a product continues to command good physician acceptance, we can afford to continue with fairly frequent samplings. Furthermore, on a really successful product, an increased tempo of our sampling operation will push sales up still further. But this latter phenomenon holds true only up to a point. Somewhere along the line, we are bound to run into diminishing returns; i.e., the additional business gained no longer supports the additional promotional expense in terms of operating profit. The exact pattern depends upon the nature of the product and the rate of sales increase, but we feel we have gained a good basis for determining the optimum campaign in any given case.

Third, testing has shown us that larger samples can increase sales, although whether they do or not depends on a good many factors, chief among these the nature of the particular product promoted. The big question that always arises is, of course, "How large should the sample be?" and the answer to this question is usually rather elusive.

There are different kinds of large samples. Where relatively long administration to a single patient is necessary to reach a definitive evaluation of the drug, as in the case of most antihypertensive agents, several commercial packages, at least in the introductory phase, may be the best answer. With a drug the beneficial effects of which, if they are to appear, appear almost immediately, sample packages which enable the physician to give out small starting supplies along with a prescription to quite a number of patients may be the appropriate method. Again, when the main objective is to impress upon the physician the availability of a range of dosage strengths or a variety of dosage forms, a box displaying a token sample of each strength or form makes an effective three-dimensional advertising presentation. The number of possibilities is great and, in the final determination, there can be no substitute for judgment based on marketing research information and the peculiarities of the product.

I thought that you might like to see a very few of these larger samples. Here's an interesting one from Ciba. The box is divided into four compartments, each with four match-book samples, each of which contain eight tablets. This mailing, promoting four closely allied antihypertensive preparations—"Serpasil," "Serpasil-Apres-

oline," "Apresoline," and "Singoserp"—helps give the doctor a good indication of which is most suitable in several individual cases of high blood pressure while, at the same time, serving as a strong reminder to him of the availability of four different preparations for the same basic condition. Here is another, this time in three compartments, each again with four match-books. But each of these match-books contains only two tablets of "Doriden," which is still a sufficient trial supply to find out if the drug will relieve insomnia in a given patient. With this sample, the drug can be tried in as many as twelve separate patients and may easily create eight to a dozen prescriptions without cutting into sales at all. This box here holds a 30-capsule "Dexamyl" *Spansule* dispenser in the form of a small round clock to emphasize day-long action. From the side of this clock comes a cellophane pull-strip holding the capsules so that the doctor can tear off two or three to tide each patient over until a prescription is filled. And this one has a two-compartmented cardboard box, from one side of which come individual cellophane sample units of six "Compazine" tablets and, from the other, individual units of four "Compazine" *Spansule* capsules—six units in each compartment. This box is labelled "Starting supply for 12 patients." Ideally, this sample mailing serves to launch a round dozen patients on a course of therapy and may easily produce a dozen original prescriptions and 24 renewals.

In the case of this large "Compazine" sample, for example, did most physicians dispense only a single unit of tablets or capsules to a single patient as a "starting supply"? In other words, do the doctors who receive such samples employ them in the way that the manufacturer intended? We've checked this point and have discovered that, for the most part, they do.

Finally, we have found that, when response to promotion levels off, it is time to cut back on sampling (and other promotion, too). We all have in our lines a number of good, substantial specialities which go on selling year after year at about the same rate. There's always the temptation to play it safe and continue to spend fairly large amounts on these products. So we have conducted a number of tests to try to determine the amount of money necessary to maintain sales volume. Over the years, we have discovered that, in many cases, we were probably being wasteful with our sampling. In chosen test areas, we have reduced the number of sample mailings and watched. First, we did this very gingerly; then, we went at it more boldly.

Now, we believe that low maintenance-type campaigns are the most economical way to handle the sampling of these well-established, bread-and-butter products.

I would like to have talked about sampling longer—the techniques involved in it, the results achieved, and the mistakes made with it, too—for there is much more to be said.

One last encouraging note on sampling: In a recent survey conducted for the American Medical Association, Taylor, Harkins & Lea, Inc., an independent research concern, found that in only 10% of the cases did physicians pass on samples to patients without being prescribers of the preparations advertised by those samples.

Before closing, I should like to comment briefly on two rather prevalent and sweeping misconceptions about ethical pharmaceutical promotion:

> First, if it were not for the expense of promotion (particularly of the advertising), the pharmaceutical industry could afford to charge much less for drugs, thus greatly lightening the financial burden of illness; and, second, pharmaceutical promotion is an ungoverned and irresponsible activity, carried out on the philosophy of sales at any price and uncontrolled by regulations from without or principles within.

As to the first of these misconceptions, we must first accept the premise that, in any industrial endeavor, the pricing of an article approaching the market is largely determined by the anticipated unit cost of its manufacture. In the pharmaceutical industry, at least, this unit cost is estimated, to a great extent, on how fully the manufacturer expects ultimately to utilize his machinery and other fixed overheads and on how rapidly he hopes to absorb or amortize the tremendous investment he has put into the research on and the development of his drug—an investment by Merck in the unparalleled case of cortisone of more than $25,000,000. This anticipated degree of utilization and rate of amortization is governed, in turn, by the output that will be required to meet a predicted volume of sales. And this sales prediction would never have been set and could never be met except in contemplation of the results of necessarily expensive promotion. I am only an advertising man but even I can see that, without the mass sales volume made possible by this expenditure on direct mail,

detailing, and medical journal advertising, drug prices would perforce be higher than they are.

As to the second misconception, pharmaceutical promotion wouldn't have a Chinaman's chance of being irresponsible and ungoverned even if it wanted to. There are, of course, minor and temporary lapses from grace and all of us at one time or another have been guilty of such lapses. But, believe me, these are brought to our attention in no uncertain terms and with the speed of a boomerang.

Externally, there is the Argus-eyed Food and Drug Administration. I can think (and I believe everyone in my fraternity would agree) of no government agency more enlightened or more cooperative. They know their own business in and out but they know, too, and are marvelously sympathetic with the special problems of the pharmaceutical industry. They point out to us pitfalls that we might never have seen and they sit down at the council table with us to suggest ways and means of overcoming our difficulties. But, for all that, they can be strict as early New England divines, sticklers for "the book," and as little likely to yield on an important technical point as a Russian commissar.

As all of you know, they can refuse to approve a new drug. What is far less well-known is that they also have jurisdiction over our advertising copy. If we refuse or even if we inadvertently fail to comply with their stipulations, not only as to the actual words themselves but also their possible implications, they can withdraw their approval of our New Drug Application.

But there is almost never an instance of any such open breach with the FDA. The pharmaceutical companies have a deep respect for the wisdom and reasonableness of this body and almost invariably either comply forthwith or work to achieve a compromise acceptable to both sides. That resort to the decision of the courts is almost unheard of is a tribute to the reciprocity between the two parties.

You may now, however, be wondering whether it is possible, as the months and years roll by, for the FDA to continue to check up on each of hundreds of direct mailings and medical journal ads. Of course it isn't. For them to do so would require a fabulously inflated staff, placing an unjustifiable burden on the taxpayer's pocketbook. But, still more important, the exercise of such a continuing censorship would not be necessary in the overwhelming majority of cases. Why not? Well, because the intelligent pharmaceutical company is

traditionally loathe to try to circumvent the FDA, to undermine in anyway the authority of this agency which it gratefully looks upon as a sharer in the burden of a heavy responsibility.

Here, just as a disgression, I might cite an incident which shows that, although the FDA does not attempt to prolong its surveillance over advertising indefinitely, it doesn't go to sleep at the switch either. More than a decade ago, one company had a topical antibiotic preparation which had been approved for just one limited indication. In a mailing sometime after introduction, an overly eager copy supervisor inserted, with the full permission of the author and the journal, reprints of a published medical article covering the use of the preparation not only in the approved indication but in certain other closely allied indications as well. Within two or three days after the mailing went out, the company heard from the FDA. Their Antibiotics Division said simply that, in the event that any such thing happened again, they would not certify the next batch. And that was in the "old days" before FDA control was nearly as stringent as it is today.

But, you may ask, what about the pharmaceutical industry when the policeman isn't looking? What evidence is there of a sense of moral responsibility within the industry itself? I could point again, without hesitation and without qualms, to the prevailingly high quality, scientific accuracy, and good taste of pharmaceutical promotion, but there is more tangible and formalized evidence than that. Two major bodies in the industry have recorded statements of ethical procedure for our own guidance and governance.

The Pharmaceutical Advertising Club of New York, whose membership numbers virtually all the executive advertising personnel of the eastern companies, was the first group to draw up such a declaration which it calls its "Code of Ethics." And the Pharmaceutical Manufacturers Association, the industry's most representative organization, last year adopted "A Statement of Principles of Ethical Drug Promotion," which puts its 140 member companies on record in the shape of a uniform code.

This latter "Statement of Principles" is very far from being merely a philosophical treatise. This is apparent in the last of its seven points, as follows: "Any violation of these principles brought to the attention of the President of the Pharmaceutical Manufacturers Association shall be referred by him to the Board of Directors." This document is exerting, and will continue to exert, a positive and

pervading influence in all pharmaceutical promotion. I recommend it to your attention. I feel that no other collective industry has promulgated anything comparable to it.

I would like to close this talk on a note of real humility. Parts of this address may have sounded to you grandiloquent; if they did, I am truly sorry. I know well that pharmaceutical promotion is far from perfect; it is a human endeavor and never will be perfect, but I think it has thrived upon criticism and will go on doing so. I can assure you that anyone who examines it closely (and I have done so) will perceive a world of difference between the advertising of ten years ago and that of today—a difference for the better. The last ten years have been notable for a growing awareness by us of our position in the American medical scene, of the millions of watchful- and sometimes hostile-eyes upon us, of the sharp questioning of our motives and ideals. We are no longer, in a sense, "private"; we have been likened to a public utility on a national scale; and our promotion, ever more and more, must promote in the words of the P. M. A. "Statement of Principles" the "public welfare," must maintain "honorable, fair and friendly relations with the medical profession, with associated sciences, and with the public."

I have been hard put to give you much more than a fleeting glimpse of ethical pharmaceutical promotion. If I have been able to convey an impression, I am happy; at least, I hope I have not confused you. Thank you for your patient attention.

A DECADE OF CHEMOTHERAPEUTIC MANAGEMENT OF MALIGNANT MELANOMA

By John R. Sampey *

MALIGNANT melanomas are not as responsive to chemotherapeutic control as are the leukemias (38), Hodgkin's Disease (39, 40), lymphosarcoma (41), or multiple myeloma (42). In a study of over 200 cases in the medical literature of the last decade, nitrogen mustards, phosphoramides, radioactive isotopes, and antibiotics play the leading roles in therapy, but the remission rates are low, and none of the dozen other agents reviewed in this study shows any great promise of improving the management of this neoplastic growth.

Phosphoramides. Triethylenephosphoramide (TEPA) and thiotriethylenephosphoramide (Thio-TEPA) account for almost one-third of the patients reviewed in this paper. Farber *et al.* (11) described two fair regressions with TEPA lasting for nine and 30 months. Downing *et al.* (10) noted one complete regression for a year with this same chemical. Tullis (44) reported two of seven patients had good regressions on TEPA therapy, and one good and one brief response in six patients given Thio-TEPA. Wright *et al.* (48) observed that leukopenia developed in 59 of 94 patients with various neoplasms on Thio-TEPA therapy, but they concluded that the drug was safe when the blood counts were watched; they recorded one moderate regression of a malignant melanoma in two patients in 1957 who were on Thio-TEPA (47) and they induced regressions in five of 16 patients in 1958. Zubrod (49) in a quantitative comparison of nitrogen mustard and Thio-TEPA therapy concluded that the former was significantly better in Hodgkin's disease and lung cancer, but not in melanoma and breast tumors. Ultmann *et al.* (45, 46) in two studies reported no regressions in 10 cases of malignant melanoma after treatments with Thio-TEPA. McIver *et al.* (22) obtained objective tumor regression in one of seven patients by persistent oxypentamethylene diethylene thiophos-

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phoramide (OPSPA) therapy but no response by intermittent doses in eight patients. Olsen (32) found Thio-TEPA was without effect in one case of malignant melanoma.

Nitrogen Mustards. Attention has already been directed to Zubrod's (49) comparison of N-mustards and Thio-TEPA. Rollins and Shaw (35) reported no response in one patient with malignant melanoma given ACTH and HN_2, and Ariel and Kanter (2) recorded no response in five patients on HN_2 alone. Marcus *et al.* (26) noted no effect of *p*-naphthyl-di-2-chloroethylamine (R48) clinically or histologically in three patients. Schwenkenbecher (43) induced a good regression for several months of a melanoma in one patient with nitrogen mustard oxide (nitromin), following x-ray therapy, but Mrazek (30) *et al.* reported no response in four cases on nitromin alone, and Hörlin and Schmitt (17) also reported failure in one case. Phenylalanine nitrogen mustard induced better results for Creech *et al.* in two studies noted good regression in five of six patients in 1958 (6), and seven good responses in eight cases in 1959 (7). Hales *et al.* (13) noted some improvement in two of eight patients on phenylalanine mustard, and Holland and Regelson (16) found objective evidence of limited benefit in two of 16 cases. Papac *et al.* (33) described transient regression in one melanoma under phenylalanine mustard therapy given intravenously but none in three cases when given orally. Ryan *et al.* (37) employed a pump-oxygenator with phenylalanine mustard and they described the disappearance of lesions in one patient over a six-months' period. Alpert (1) stated that sulfur mustard was ineffective in malignant melanoma.

Radioisotopes. Marcus and Rotblat (25) noted some inhibition in the growth of multiple melanomata after radiophosphorus treatment but no change in the clinical course of one patient. Lederman (21) recounted the use of radiophosphorus and radiostrontium in the treatment of 18 patients with malignant melanomata of the eye; he reported 12 were alive and well at the time of writing and that three had been so for three years. Olmsted and Bierwaltes (31) used thyroidectomizing doses of radioiodine in eight patients but he found no effect of the isotope on growth of the malignant melanomas; Kory *et al.* (19) also reported no alteration in the course of this disease in eight patients under similar therapy.

Antibiotics. Gregory (12) cited good regressions in two patients with malignant melanoma after the administration of *Bacillus Subtilis* as an antibiotic. In 1956, Magill *et al.* (23) reported transient benefit in one case of melanoma after the use of 6-diazo-5-oxo-1-norleucine (DON) but, the next year, he found no regression with DON in five patients. In two studies on actinomycin D, Moore *et al.* (28, 29) recorded 50% regressions in two melanoma patients and some improvement for 30 days in one of eight cases.

Miscellaneous Agents. Rothmann and Klein (36) described necrosis of metastases in malignant melanoma in a comparative study of plenosol and urethan, and Krementz *et al.* (20) observed regression in 13 of 15 patients with metastatic melanoma after the use of PAM and TSPA. Mihaylov *et al.* (27) cited no improvement in four patients on triethylene melamine (TEM) therapy, and Hambly and Robertson (15) noted none in two cases treated with TEM. Colsky *et al.* (5) found some antineoplastic action of guanazolo in one patient. Burchenal *et al.* (3) concluded that folic acid antagonists were without effect on three patients with melanoma and that 6-mercaptopurine (6-MP) was also ineffective in one case tested (4). Hall *et al.* (14) also recorded no results with the antimetabolite, 6-MP, in two cases. Hyman and Gellhorn (18) reported no improvement in one case of melanoma treated with myleran, and Pearson and Eliel (34) noted no response to ACTH/cortisone therapy in one case. In two investigations, Curreri (8, 9) recorded no improvement in patients with malignant melanoma who received treatment with 5-fluorouracil.

Summary

Table I summarizes the chemotherapeutic control of melanomas. Phosphoramides and nitrogen mustards account for 60% of the clinical trials, but the number of good responses in the former is disappointingly low. Radioactive isotopes occupy a unique place in these preliminary trials. It is noteworthy, also, that chemicals which have played such a commanding role in the management of the leukemias, lymphomas, and reticuloses; namely, folic acid antagonists, steroid hormones, 6-MP, P^{32}, and TEM, are strikingly ineffective in melanomas judging from the limited trials of the last decade.

TABLE I

CHEMICAL MANAGEMENT OF MALIGNANT MELANOMA

Chemicals	*No. of Cases*	*No. of Remissions*		*No. of References*
		Good	*Fair*	
Phosphoramides	60	5	9	5
N-mustards	58	15	5	12
Isotopes	35	12	1	4
Antibiotics	18	2	4	4
Miscellaneous	30	—	14	11

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SELECTED ABSTRACTS

A Study of the Filtration of Bacteriophage. Jordana, Roman de Vicente. *Applied Microbiol. 7:239* (1959). A study was made of the effect of filters upon the removal of filterable phage from bacterial suspensions. Overnight suspensions of *Bacillus polymyxa* phage or *Escherichia coli* phage were passed through several filters under various conditions. The number of phages in the original suspension was compared with the number in the filtrate. Standard media were used to avoid as much as possible the interference of unknown factors. Filters used were Chamberland candles 5L3 and 5L5, sintered glass plates 5/3 from two sources, and Seitz EK pads from 3 sources.

Many interesting results were obtained from the study of these filtrations. A preliminary vacuum filtration of 10 ml. of phage suspension through each of the filters showed that adsorption was negligible for sintered glass plates and Chamberland filters but quite pronounced for Seitz pads. One Seitz pad source showed greater adsorption than another. Repeating the filtrations at various pH values for the suspension again showed that adsorption was negligible for the sintered glass and Chamberland filters. However, a Chamberland filter not cleaned by ignition to white heat between uses showed a significant increase in adsorption with each succeeding use.

With Seitz EK pads, there was practically complete adsorption over the acid pH range employed but at the alkaline range a small number of particles were allowed to pass through. Although there was some evidence of differences among the asbestos pads from different sources, further studies seemed to indicate that this was not significant. Further studies with Seitz pads showed that small surface area filters allowed more phage particles to pass through, and increasing the volume of solution filtered increased the number of particles passed through. Fractional filtration showed that the first filtered aliquots gave greater adsorption than subsequent aliquots. Again, acid suspensions yielded less particles in the filtrate than did alkaline suspensions. It was also found that the pH of the filtrate was somewhat higher than that of the unfiltered suspension.

Continuing the study of the effect of Seitz pads on the removal of phage particles, it was found that variations in the negative pressure affected the results. Different sources of vacuum, which produced differences in negative pressure and the rate at which the maximum

was attained, produced differences in adsorption. Also, lower filtration pressure differentials produced greater adsorption than higher pressure differentials. Estimates of maximum yield of particles in the filtrates under a constant vacuum of 650 mm. of mercury over the pH range of 5.9 to about 7.5 showed that the pH of maximum yield was about 6.85. When 50 ml. of suspension was filtered, over 95 per cent of particles were obtained in the filtrate whereas total adsorption occurred when 10 ml. of suspension was filtered through an identical filter at a pH of 5.9.

Local Treatment of Plantar Verruca by Injection of Vitamin A. Gilbert, R. S., and Williams, M. J. *U. S. Armed Forces Med. J. 10:*843 (1959). The oral administration of large doses of vitamin A has shown encouraging evidence of the disappearance of warts. Accordingly, the authors experimented with the injection of an aqueous preparation of vitamin A into the wart. The authors indicated that the dose should not exceed 0.1 ml. per square centimeter of verrucose area. If further injections were necessary, they were given at weekly intervals with the dosage increased up to 0.3 ml. To provide anesthesia, about 1 ml. of a 1 per cent solution of xylocaine hydrochloride and 1:100,000 epinephrine was injected under the lesion.

The most dramatic result was the relief from pain. In 95 per cent of the patients, freedom from pain was experienced after the first or second injection. Involution of the wart began within a few days after the first injection. Eighty-two of the 100 patients treated showed complete resolution of the wart within a few weeks. All of the patients were followed for at least six months following the regression of the lesion. Five patients required only a single injection although the average number of injections was 4.2. Only a few reactions were encountered and these were confined to itching around the site of injection. No recurrences were observed. An additional advantage of this treatment was that the patients remained completely ambulatory throughout treatment with no bulky bandages or change in bathing habits required.

The preparation employed contained 50,000 units of vitamin A palmitate per ml. with dl-α-tocopherol and butyl hydroxyanisole as antoxidants, Polysorbate 80 as a solubilizer, and chlorobutanol as a bacteriostatic agent in a citrate-phosphate buffer.

BOOK REVIEW

Hormones and Atherosclerosis. G. Pincus. xvi + 484 pp. Academic Press, Inc., New York 11, N. Y., 1959. Price: $13.50.

An impressive contribution to the rapidly expanding literature on the topic most prominent in the minds and conversation of both scientists and laymen is an appropriate description of this volume.

The subject matter presented in this book covers verbatim the papers and discussions of a conference held at Brighton, Utah, sponsored by the Endocrinology Study Section of the National Institutes of Health.

Prominent academic, industrial, and clinical investigators assembled at this meeting to interchange information and compare their views of hormonal influences on the progression of atherosclerotic disease states. The foremost consideration predominant throughout the presentations and discussions was the question of the therapeutic application of hormones in this condition.

For convenience, the material was divided into five major categories: cholesterol metabolism, hormones in lipogenesis and transport, the influence of various hormones on experimental atherosclerosis, the interrelationship of blood lipids and endocrines in animals and man, and finally clinical-biological interactions pertaining to endocrine influences.

Clear and concise tabular and graphic illustrations, liberally incorporated, exemplify the information of the text.

For individuals involved in research or with the therapy of atherosclerosis, this book offers an up-to-the-minute picture of the importance of endocrine factors. It emphasizes both the knowledge available on current concepts and the problems which still remain to be explored.

THOMAS H. F. SMITH

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The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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